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August 27, 2002

Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research
Food and Drug Administration
HFD-1
Woodmont Office Complex 2
1451 Rockville Pike,
Rockville, MD 20857

Re: **Determination of Regulatory Review Period for NEXIUM, Docket No. 01E-0365**

Dear Dr. Woodcock,

We submit his letter on behalf of Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. (collectively "Reddy") in response to the Notice of the FDA Determination of Regulatory Review Period for Purposes of Patent Extension regarding NEXIUM® published in the Federal Register on Thursday, February 28, 2002, Vol. 67, No. 40, pages 9299-9300.

Reddy requests that the FDA reconsider the regulatory review period determination and decline the patent term extension petition for U.S. Patent No. 4,738,974 (the '974 patent) due to a total lack of due diligence by AstraZeneca

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(hereinafter "Astra") in seeking FDA approval of the product claimed in the '974 patent during the regulatory review period for NEXIUM®. The product claimed in the '974 patent is not equivalent to the active ingredient of NEXIUM® and was not subject to the regulatory review period for NEXIUM®. Therefore, Astra has not exhibited due diligence with respect to the products claimed in the'974 patent during the regulatory review period and the determination of the amount of time for restoration should be recalculated and reduced to zero days.

a. Background

Astra listed the '974 patent in the Orange Book for NEXIUM®. On October 2, 2001, the FDA advised the Patent and Trademark Office that Astra had applied for a patent term extension on the '974 patent requesting an 865 day extension. On February 27, 2002, the FDA released the calculated review period as 865 days. Reddy maintains that this calculation was erroneous. Astra did not act with due diligence in seeking FDA approval of the product claimed in the patent for which an extension has been sought during the regulatory review period for NEXIUM® because the '974 patent does not cover the active ingredient in NEXIUM®. Accordingly, the regulatory review period determination made for the patent term extension petition for the '974 patent should be reconsidered due to lack of due diligence and the amount of time restored recalculated to the appropriate zero days.

b. Relevant Provisions Of The Hatch-Waxman Act

The Hatch-Waxman Act grants a limited extension of the patent term for a product which was withheld from the market during the patent term because of delays in obtaining FDA approval for the product. The Hatch-Waxman Act provides in section 156(b)(1), that, "the rights derived from any patent the term of which is extended under this section shall during the period during which the term of the patent is extended . . . in the case of a patent which claims a product, be limited to any use approved for *the product* . . . ." 35 U.S.C. § 156 (b)(1) (emphasis added). Section 156(b)(2) states in pertinent part, that "in the case of a patent which claims a method of using a product, be limited to any use claimed by the patent and approved for *the product*" 35 U.S.C. § 156(b)(2) (emphasis added). Section 156(f)(1) defines "product" to mean "drug product." Section 156(f)(2)(A), in turn, defines "drug product" to mean *the active ingredients* or any salt or ester of the active ingredient. *Glaxo Operations UK Ltd. v. Quigg*, 894 F.2d 382, 400 (Fed. Cir. 1990)(construing term "product"). Astra has stated that both the approved product and the active ingredient are "esomeprazole magnesium." (See attachment 1).

c. The Product Claimed In The '974 Patent Is Not NEXIUM®.

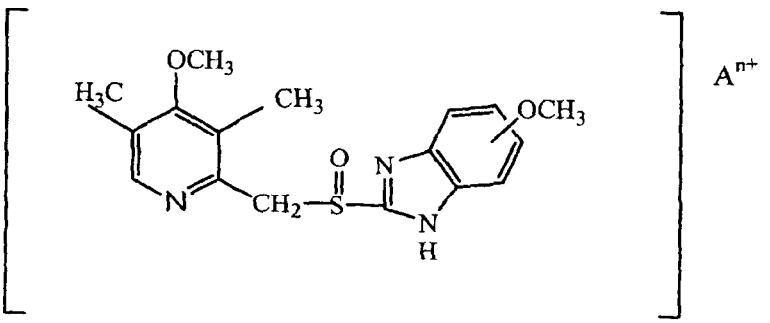
The approved product or active ingredient claimed in the '974 patent is not the "same" as – i.e., "identical" to – the active ingredient in NEXIUM®. The labeled active ingredient in the approved NDA for NEXIUM® is esomeprazole magnesium, esomeprazole being the S or (-) isomer of omeprazole (See attachment 1). The

compound claimed in the '974 patent is omeprazole magnesium, which is limited to the racemic mixture of both enantiomers and contains an equal mixture of both the R and S isomers (See attachment 2). Racemic omeprazole in a neutral, non-salt, form was previously approved under a separate NDA and is marketed as PRILOSEC® (See attachment 3). Indeed, in Astra's PTE application, it admitted that "esomeprazole magnesium is a different active ingredient from omeprazole, which is marketed as Prilosec® (NDA 019810), for which a patent term extension has previously been granted." Furthermore, the fact that the FDA lists omeprazole and esomeprazole separately in the Orange Book is a clear indication that the active ingredients are not the same.

Reddy is not asking the FDA to review the substantive patent issues involved in claim construction. Instead, the FDA need only rely on Astra's own statements in related applications which clearly show that the claims of the '974 patent do not cover NEXIUM®.

Claim 1 of the '974 patent, the only independent claim, claims:

A compound of the formula



wherein n is 1, 2, or 4; and A^{n+} is Li^{+}, Na^{+}, Mg^{+2}, or Ca^{+2}.

Claim 1 does not state that it covers either enantiomer separately. In fact, there is no mention of the enantiomers throughout the specification. The file history of the '974 patent is also silent as to the separation, preparation, or use of the enantiomers as opposed to the racemic composition. Plainly the '974 patent covers omeprazole magnesium – the racemic form.

U.S. Patent No. 5,714,504 (the '504 patent) is also listed in the Orange Book for NEXIUM® (See attachment 4). The '504 patent was filed on January 23, 1995, issued on February 3, 1998, and is assigned to AstraZeneca. The '504 patent claims:

> A pharmaceutical formulation for oral administration comprising a pure solid state alkaline salt of the (-) enantiomer of 5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole and a pharmaceutically acceptable carrier.

This claim is clearly discloses the (-) isomer of omeprazole as a salt.

During the prosecution of the '504 patent, the Examiner rejected the pending claims as obvious over EP 124,495 (See attachment 5). The '974 patent is the U.S. equivalent of EP 124,495. The Examiner stated that the individual isomers were obvious variants over the corresponding racemate because of their presence in the racemate. Astra responded to the rejection by stating that EP 124,495 did not disclose or suggest a formulation comprising the salts of a single (-) enantiomer of omeprazole (See attachment 6, beginning at page 6). Furthermore, Astra continually asserted that the activity of the (-) enantiomer was superior to the activity of the racemic mixture. "The EP

reference discloses racemic forms of benzimidazoles but is silent on how to prepare single enantiomers or any of their properties." (See attachment 5, at page 11). As stated by Astra, the claims of the '974 patent are not intended to encompass the individual enantiomers. Therefore, the product claimed in the '974 patent is the racemic omeprazole salt and not the (-) enantiomer, which is the active ingredient in NEXIUM®.

d. The Product Claimed In The '974 Patent Is Not Equivalent To NEXIUM®.

The product claimed in the '974 patent and the active ingredient in NEXIUM® not only differ chemically, but also differ as to their clinical effect. During the prosecution of the '504 patent, Astra demonstrated to the Examiner's satisfaction that the (-) enantiomer of omeprazole reduced the interindividual variation in plasma levels, as measured by AUC, in slow and rapid metabolisers. (See attachment 5, pages 5-9). The result, according to Astra, is higher plasma levels of the drug at the same dosage level of the prior art. Id. Therefore, Astra claims that the salts of the (-) enantiomer and the racemic compound do not have the same clinical profile when administered to patients. Id.

During the prosecution of the '504 patent, Astra submitted the declaration of Dr. Tommy Andersson (See attachment 7). The declaration describes in detail a comparative analysis between racemic salts of omeprazole and the (-) enantiomer of omeprazole salts. (See Exhibit 7, pages 6-14). The data purported to demonstrate that the difference in AUC between slow and rapid metabolizers was 30-fold for (+) or R omeprazole, 10-fold for racemic omeprazole, and 3-fold for (-) or S omeprazole. Id. The study also found that the average AUC in the majority of the population is two-fold higher for the (-)-

enantiomer of omeprazole than for the racemic mixture. Id. The results also purported to demonstrate a higher dose efficiency and affords a longer time of post-dosage acid inhibitory effect. Id. Therefore, according to Astra, the racemic and (-) enantiomer magnesium salts of omeprazole are not equivalent.

e. The '974 Patent Does Not Qualify For An Extension With Respect To The Regulatory Review Period Of NEXIUM®.

The extension of a patent term is allowed under 35 U.S.C. §156 (a)(4) for "a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended in accordance with this section from the original expiration date of the patent, which shall include any patent term adjustment granted under section 154(b), if the product has been subject to a regulatory review period before its commercial marketing or use. . . The product referred to in paragraphs (4) and (5) is hereinafter in this section referred to as the "*approved product*"." (emphasis added). The regulatory review period, which is defined in 21 C.F.R. § 60.22, is the sum of the lengths of the testing phase and approval phase. However, due diligence is required of the applicant during the regulatory phase in order to merit an extension or restoration of lost time.[1] Due diligence requires that the applicant exhibit the degree of attention, continuous directed effort, and timeliness that would ordinarily be expected during the FDA regulatory period.[2]

[1] 35 U.S.C. § 156(d)(2)(B).
[2] See 21 C.F.R. § 60.36(a).

Under current FDA interpretations of the statute, a patent term extension may be granted only on a patent claiming the active ingredient or any salt or ester of the active ingredient. In the case of NEXIUM®, this would mean that a patent term extension could only be granted on a patent covering esomeprazole magnesium, or a salt or ester with esomeprazole magnesium. As set forth above, the claims of the '974 patent cover neither. Consequently, any "product" claimed in the '974 patent was not subject to the regulatory review period for NEXIUM®, and it can not be said that Astra acted with due diligence in seeking FDA approval of any "product" claimed in the '974 patent with respect to NEXIUM®. For that reason, the '974 patent does not merit restoration of any time.

e. Conclusion

For the reasons presented above, Reddy requests that the determination of the regulatory review period for the '974 patent term extension petition be recalculated and adjusted to zero.

Respectfully submitted,

Bruce D. Radin

Copy to
David Brennan

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INDEX OF EXHIBITS

1. NDA labeling information submitted for NEXIUM®
2. U.S. Patent No. 4,738,974
3. NDA labeling information submitted for PRILOSEC®
4. U.S. Patent No. 5,714,504
5. Office Action issued during prosecution of the U.S. Patent No. 5,714,504
6. Response to Office Action of Exhibit 6
7. Declaration of Dr. Tommy Andersson, submitted during the prosecution of U.S. Patent No. 5,714,504